
From: Matthew Day </O=TEVA/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=MDAY>
To: Abbas Ebrahim, MD
Sent: 1/8/2015 1:55:20 PM
Subject: PAIN-40128_PM ERSG Video Script_TO CLIENT_01 07 15.docx
Attachments: PAIN-40128_PM ERSG Video Script_TO CLIENT_01 07 15.docx

Hi Abbas,

Attached is an example of how we need to rewrite the document prior to PARC submission.

Can you work on this in the morning and we can touch base at lunch.



I now have a forecast meeting at 9am.

Sorry for the inconvenience,





Matt

PLAINTIFFS TRIAL
EXHIBIT
P-19080_00001

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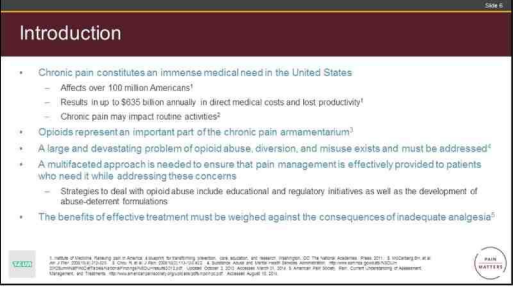
Part 1 – Program Introduction and Overview		
#	Slide	Narration
1		<p>Gudin Hello, my name is Jeff Gudín. I'm the director of pain management and palliative care at the Englewood Hospital and Medical Center in Englewood, New Jersey, and also a clinical instructor of anesthesiology at the Icahn School of Medicine at Mount Sinai.</p> <p>I want to welcome you to our program, titled "Evolving Roles, Same Goals: The Changing Landscape of Pain Management."</p>
2		<p>Gudin Before we get started, I want to introduce you to our faculty for the program.</p> <p>Argoff I'm Charles Argoff, a professor of neurology at Albany Medical College and director of the Comprehensive Pain Center at Albany Medical Center in Albany, New York.</p> <p>Brennan I'm Michael Brennan. I'm the medical director and chief medical officer of the Pain Center of Fairfield in Fairfield, Connecticut. I'm also associate medical director for the Chronic Pain and Recovery Center at the Silver Hill Hospital in New Canaan, Connecticut.</p> <p>Gudin Welcome gentlemen.</p> <p>Argoff and Brennan Glad to be here.</p>

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3	<div data-bbox="224 381 727 659"> <div>Slide 3</div> <div>Disclosures</div> <ul style="list-style-type: none"> This promotional program was developed by Teva and the faculty are presenting on behalf of Teva The faculty have received compensation from Teva to make this presentation <div>   </div> </div>	<p>Gudin</p> <p>I also want to let you, our audience, know that this program was developed by Teva Pharmaceuticals, that the three of us are presenting on behalf of Teva, and that we have been compensated by Teva to develop this presentation.</p>
4	<div data-bbox="224 735 727 1009"> <div>Slide 4</div> <div>Program Overview</div> <ul style="list-style-type: none"> Today's Objectives: <ul style="list-style-type: none"> Outline some of the options for pain management, focusing on the role of opioids <ul style="list-style-type: none"> Although efficacious, opioids are subject to misuse, abuse, and diversion Consider the role of HCPs, patients, and government as part of a multifaceted approach to address these issues Discuss how industry may play a role in augmenting a multi-faceted approach through the development of abuse-deterrent opioid formulations <ul style="list-style-type: none"> Review FDA draft guidance on their development <div>   </div> </div>	<p>Gudin</p> <p>Over the course of this program, we will discuss some of the issues we all deal with on a day-to-day basis. Specifically, we'll take a look at treatment options, focusing on opioids. As we all know, opioids are used to treat pain commonly efficacious, but abuse can occur are subject to misuse, abuse, and diversion. As such, it's important that we, as pain practitioners, understand when and how to use them.</p> <p>We will also examine a multifaceted approach to addressing issues associated with opioids, and how HCPs, patients, and the government can help in safeguarding medications.</p> <p>Finally, we'll take a look at how the development of abuse deterrent opioids may play a role in this multifaceted methodology, taking information from the 2013 FDA Draft Guidance on this topic.</p>

Comment [MD1]: How do you safe guard medicines?

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Part 2 – Complexities in Pain Management	
5	<div>  </div> <div> <p>Gudin</p> <p>Hi, I'm Jeff Gudim and I am going to start this program by talking about some of those day-to-day challenges a practitioner may face when it comes to prescribing opioids.</p> </div>
6	<div>  </div> <div> <p>Gudin</p> <p>Chronic pain constitutes a significant medical need in the United States. We recognize that patients are living longer with chronic illness, surviving their trauma or cancer, and suffering with multiple comorbidities that all have pain in common.</p> <p>We know that pain affects over 100 million Americans and costs this country a significant amount of money, estimated at over 600 billion dollars annually in direct costs and lost productivity. And we know that there's a cost to patients as well, that chronic pain may impact routine activities.</p> <p>Now, we know there are a few choices for analgesic medications, and opioid analgesics represent an important tool in our chronic pain arsenal. Unfortunately, with the expanding use of opioid analgesics, an epidemic of prescription opioid abuse has resulted due to the diversion of these powerful analgesics to the non-patient population.</p> <p>One of the challenges for those of us</p> </div>

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	<p>who treat pain patients has been how to utilize these important analgesics safely and effectively. And what we've recognized is that there's no simple solution. A multifaceted approach is needed to make sure that pain management is adequately provided to patients who need it, while we also deal with issues such as abuse, misuse, and diversion of these substances.</p> <p>We've developed strategies to deal with opioid abuse, most notably focused around educating the many parties involved. The pharmaceutical industry has also stepped up and is trying to play a role in preventing the misuse and abuse of prescription analgesic medications.</p> <p>One way that they've done this is through the development of abuse deterrent formulations. And any time we treat patients, always in the back of our heads as clinicians is, we have to balance our treatments. So we have to provide patients with adequate analgesia, but minimize the adverse events associated with those medications, and not just physiological adverse effects, but also the adverse effects of opioid abuse, misuse, and/or diversion.</p>
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Opioids An Important Analgesic Option

Opioid Prescriptions Dispensed by Retail Pharmacies—United States, 1991–2013

Year	Total Prescriptions (millions)
1991	76
1992	79
1993	82
1994	85
1995	87
1996	88
1997	91
1998	94
1999	97
2000	106
2001	110
2002	126
2003	138
2004	142
2005	149
2006	155
2007	174
2008	184
2009	196
2010	202
2011	210
2012	218
2013	207

Department of Health and Human Services, National Center for Health Statistics, Prescription Drug Abuse and Misuse Research, 10/10/14. CDC, Division of Health Statistics and Data Services. <http://www.cdc.gov/drugoverdose/pain/painmatters/painmatters.pdf>. Accessed August 2, 2014.

DATA MATTERZ

Gudin

I mentioned before that opioids are certainly an important analgesic option in the chronic pain management world. This has been recognized over time. And if you look at this chart, starting in the early 1990s, taking us up to 2013, you could see that there has been a slow, yet progressive increase in the amount of opioids dispensed by retail pharmacies in the United States. Again, this has to do with our improved abilities to assess pain and our willingness to treat chronic pain with a treatment regimen that includes opioids.

Unfortunately, the greater volume of opioid analgesics has also resulted in issues related to misuse or diversion of these important analgesics.

8

Unintended Consequences of Abuse

Drug Overdose Deaths by Major Drug Type—United States, 1999–2010

Year	Opioids	Heroin	Cocaine	Benzodiazepines
1999	~4,000	~1,000	~1,000	~1,000
2000	~4,500	~1,200	~1,200	~1,200
2001	~5,000	~1,400	~1,400	~1,400
2002	~6,000	~1,600	~1,600	~1,600
2003	~7,000	~1,800	~1,800	~1,800
2004	~8,000	~2,000	~2,000	~2,000
2005	~10,000	~2,200	~2,200	~2,200
2006	~12,000	~2,400	~2,400	~2,400
2007	~14,000	~2,600	~2,600	~2,600
2008	~15,000	~2,800	~2,800	~2,800
2009	~16,000	~3,000	~3,000	~3,000
2010	~16,500	~3,200	~3,200	~3,200

Source: National Center for Disease Control and Prevention, Division of Health Statistics and Data Services, Prescription Drug Abuse and Misuse Research, 10/10/14. CDC, Division of Health Statistics and Data Services. <http://www.cdc.gov/drugoverdose/pain/painmatters/painmatters.pdf>. Accessed August 2, 2014.

DATA MATTERZ

Gudin

Beyond increased misuse and diversion, there has also been an increase in deaths due to drug overdose. As you can see in this chart, prescription opioids outrank both heroin and cocaine combined as a cause of death here in the United States.

Looking at the slope of these curves, you see that drug overdose deaths due to prescription opioid use has outpaced heroin and cocaine, highlighting the need to develop strategies to prevent prescription opioid misuse and abuse.

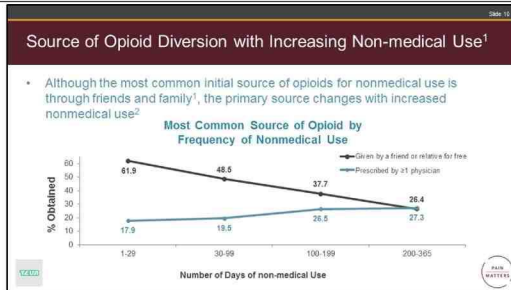
It's important for clinicians to recognize that the majority of these deaths are unintended. These are not suicide attempts. These are

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		<p>people who escalate their doses of opioids, usually combined with alcohol or other central nervous system depressants, and unintentionally die because opioids contributed to their respiratory depression.</p>
9	<p>Slide 9: What Is the Scope of Intended Abuse/Addiction?</p> <ul style="list-style-type: none"> Data derived from an evidence-based review of chronic pain patients with nonmalignant pain receiving chronic opioid analgesic therapy 67 studies that evaluated <ul style="list-style-type: none"> Abuse/addiction rate (24 studies, n=2507) Aberrant drug-related behaviors (ADRBs) (17 studies, n=2498) Urine test results (5 studies, n=1905) 25x lower rate of abuse/addiction in patients without a prior history (0.19% vs 5.0%) <p>Percent of patients being treated with chronic opioid therapy with high likelihood of abuse/addiction: 3.27%</p> <p>Source: Fishbain DA, et al. Pain Med. 2010;11(12):1940-50.</p>	<p>Gudin</p> <p>David Fishbain, a renowned academic pain psychiatrist from the University of Miami, conducted an evidence-based review of the chronic pain literature, focused on patients with non-cancer and non-malignant pain who were receiving chronic opioid analgesic therapy. He looked at 67 different studies that evaluated the abuse or addiction rate, aberrant drug-related behaviors, and urine toxicology testing.</p> <p>And what he found is that only 3.27 percent of patients being treated with chronic opioid therapy had a high likelihood of abuse or addiction with their opioid analgesics. Most notably, he found a 25 times lower rate of abuse or addiction in patients who didn't have a prior history of abuse or addiction.</p> <p>This is an important data set for us to recognize that the risk is clearly greater in patients with a previous history of abuse or addiction and that it's relatively low for patients with chronic non-malignant pain who don't have a previous history of addiction.</p>

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Gudin


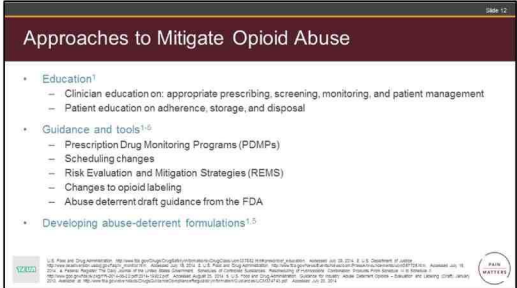
Here we see data from the Substance Abuse and Mental Health Services Administration, or SAMHSA.

We all know that the most common initial source of opioids for nonmedical use comes from a friend or family member for free, but as the frequency of non-medical use increases, the opioid becomes more likely to come from a clinician, highlighting the need for us to educate and empower our patients to use their medication appropriately.

This brings us to the end of our discussion on some of the complexities clinicians face in pain management, and I hope you found this chapter informative.

Please return to the main menu and select the next chapter to hear Dr. Argoff tell you more about the role that clinicians and others can play in addressing opioid abuse.

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Part 3 – Addressing Opioid Abuse: A Multi-Faceted Approach	
11	<div>  </div> <div> <p>Argoff</p> <p>I'm Charles Argoff, a professor of neurology at Albany Medical College and director of the Comprehensive Pain Center at Albany Medical Center in Albany, New York.</p> <p>In the previous chapter, you heard Dr. Jeff Gudin discuss some of the challenges we face with balancing the need for effective pain management with some of the dangers of prescription opioid use. To continue this conversation, I'll focus on how we can address opioid abuse with a multifaceted approach.</p> </div>
12	<div>  </div> <div> <p>Argoff</p> <p>There are many approaches to mitigate opioid abuse, and I would like to divide them into three main buckets.</p> <p>First, it's education that ensures clinicians understand how to prescribe, screen, monitor, and manage patients appropriately with opioid therapy. This should be combined with patient education on adherence to a treatment program, as well as appropriate storage and disposal of opioids.</p> <p>Second is the availability and use of tools that can help us guide the approach to managing a person on opioid therapy. For example, prescription drug monitoring programs, which have been developed in almost every state, help us as clinicians see what controlled substances our patients are currently being prescribed. We have also had scheduling changes</p> </div>


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		<p>regarding opioid therapy. We have risk evaluation and mitigation strategies or REMS programs to help us guard against opioid abuse, changes to opioid labeling, and abuse deterrent draft guidance from the FDA.</p> <p>The FDA draft guidance outlines how abuse deterrent properties can be tested and what claims the FDA might allow in the product's package insert based on favorable study results.</p>
13		<p>Argoff</p> <p>It's important to recognize that there are multiple stakeholders who are involved in addressing opioid abuse and it is necessary for there to be a collaborative approach among these groups.</p> <p>These groups include healthcare professionals who are currently involved in managing patient care, the patients themselves, State and Federal government entities, as well as industry. To ensure safe and effective pain management, we need a multifaceted approach between all parties to recognize and mitigate the risks associated with opioid use.</p>
14		<p>Argoff</p> <p>Healthcare providers can play a role by following universal precautions, incorporating screening strategies, and monitoring patient adherence to prescription opioids.</p> <p>Some of the elements of universal precautions are outlined here, and include establishing a diagnosis, incorporating the use of a treatment agreement, periodic pain assessments, reviewing the diagnosis,</p>

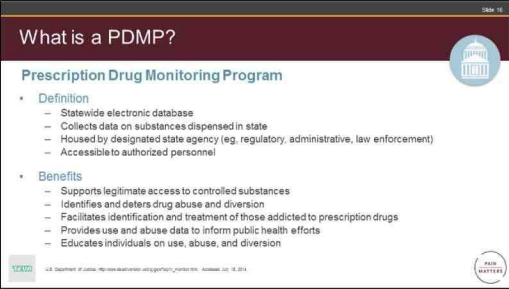
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	<p>and of course, ensuring appropriate documentation.</p> <p>Establishing the diagnosis is important to understand the medical reason for opioid therapy in the patient.</p> <p>Treatment agreements between the prescriber and the patient are also part of universal precautions and ensure both parties understand and agree to how pain will be managed.</p> <p>Assessing the pain itself, not only the character of the pain but the intensity of the pain, the impact that that pain has on that person's life, vocation, recreational activities, and so on is also part of this process.</p> <p>Reviewing diagnoses as we take care of patients over a period of time is also warranted, particularly when other treatments and diagnoses change.</p> <p>Documenting all of these is critical as well to ensure all clinicians involved in patient care understand why and how treatment decisions have been made with regard to opioid therapy in this individual.</p> <p>In terms of screening, there are various instruments that we could use as healthcare providers to identify risk of opioid abuse in our patients, and some of them are listed here.</p> <p>We also have adherence monitoring approaches. State-specific prescription drug monitoring</p>
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		<p>programs provide us with some insight into the use of opioids by a particular patient, but may vary widely between states.</p> <p>Random drug screens are important. Random urine drug screens may be a way of confirming or evaluating adherence for the people to whom we prescribe medications, as is pill counting to see whether it appears that the person who we're prescribing the medication to is actually using it in a way that we have prescribed it and is adhering to that regimen.</p> <p>Keep in mind, even though we might consider any of our patients to be low risk for opioid abuse, no patient has zero risk of it. As healthcare providers, we are the front line against opioid abuse, and as such, we need to use multiple methods to support safe and effective use of the treatments we prescribe.</p>
15	 <p>Patient Responsibilities</p> <ul style="list-style-type: none"> Safe Use¹ <ul style="list-style-type: none"> Take medications as prescribed Understand risks Awareness of inappropriate use Safe Storage^{1,2} <ul style="list-style-type: none"> Keep opioids hidden or locked to avoid access by family or friends Never share opioids with others Safe Disposal¹ <ul style="list-style-type: none"> Opioids may be disposed of through community-sponsored take-back programs If not available, environmentally friendly disposal should be undertaken per Office of Drug Control National Policy recommendations <p><small>1. American P. D. State B. Managing chronic pain with opioids: a call for change. December 2013. http://www.opioidtreatmentandprevention.org/programs. Accessed July 25, 2014. 2. Rogers K. Code 85. News Physician. 2014;8(5):52-7.</small></p>	<p>Argoff</p> <p>The patient has responsibilities as well, which we can help through patient education. For example, we can help the patient understand how to safely use, store, and dispose of opioids.</p> <p>From a safe use point of view, we can encourage our patients to take their medications as prescribed, to understand the risks associated with chronic opioid therapy, and to be aware of inappropriate use and its consequences.</p> <p>From a safe storage point of view, we don't want a person's opioid therapy</p>

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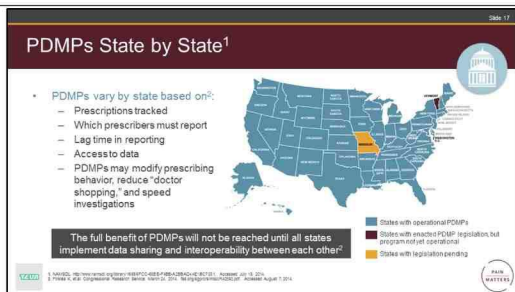
		<p>to be in the hands of their child or an animal or a family member who shouldn't be using it or a friend who is visiting because that could be dangerous. Just a single dose can be very dangerous to someone who is not supposed to be using an opioid analgesic.</p> <p>So opioids should be locked or hidden to avoid access by family or friends and of course our patients need to know never to share their opioids with others because again, a single dose can be regrettably but realistically catastrophic with respect to adverse outcomes, including death.</p> <p>Safe disposal is also very important. There are increasing numbers of community-sponsored take-back programs so opioids in a particular community may be disposed of through this approach and if that's not available, the Office of Drug Control national policy recommendations have been established and can be accessed to allow for an environmentally friendly disposal approach to these medications, which often involves taking the medication and disposing of it with coffee grounds or cat litter.</p>
16	 <p>What is a PDMP?</p> <p>Prescription Drug Monitoring Program</p> <ul style="list-style-type: none"> • Definition <ul style="list-style-type: none"> – Statewide electronic database – Collects data on substances dispensed in state – Housed by designated state agency (eg, regulatory, administrative, law enforcement) – Accessible to authorized personnel • Benefits <ul style="list-style-type: none"> – Supports legitimate access to controlled substances – Identifies and deters drug abuse and diversion – Facilitates identification and treatment of those addicted to prescription drugs – Provides use and abuse data to inform public health efforts – Educates individuals on use, abuse, and diversion <p><small>U.S. Department of Justice, https://www.ojp.gov/odc/pain/pain-matters, Accessed July 16, 2019.</small></p>	<p>Argoff</p> <p>So what exactly is a prescription drug monitoring program? By definition it is a statewide electronic database and it is designed to collect data on substances dispensed in that particular state. It is housed within a designated state agency, so it could be a regulatory, administrative or law enforcement agency; this may vary</p>

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	<p>from state to state and it's accessible only by authorized personnel.</p> <p>For example, in New York state, for me to access our database I need to have a special identification number and password and I have to file an application to become an authorized user of the PDMP.</p> <p>What are the benefits? Well, this is a program that allows us to see what controlled substances a specific patient may be receiving in that state and in that way it helps to support legitimate access to controlled substances.</p> <p>PDMPs may also be able to help identify and deter drug abuse and diversion. They may be able to facilitate identification and treatment of those addicted to prescription drugs by detecting certain patterns, which can be very helpful in cases where addiction is not obvious.</p> <p>They also allow you to establish that you will be monitoring every patient's opioid use patterns.</p> <p>They may provide use and abuse data to support public health efforts in a more global way and it certainly helps to educate all of us, especially our patients, on how to effectively use medications and how we can all play a role in limiting abuse and hopefully reduce diversion.</p>
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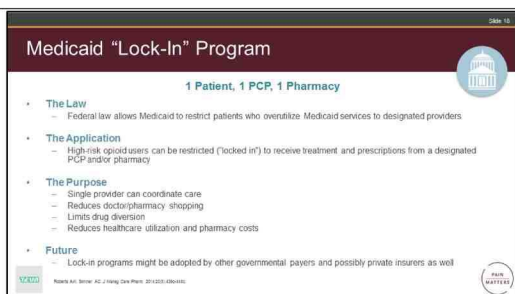
Argoff

As you can see, Missouri is the only state currently without an enacted prescription drug monitoring program and most other states have an operational prescription drug monitoring program.

PDMPs vary state by state, but in general they all are constructed to help clinicians understand how patients use prescription opioids, which may then impact our prescribing behavior. This can be used to help reduce doctor shopping and to promote higher levels of safety.

It's also fair to say that the full benefit of prescription drug monitoring programs will not be reached until all states implement data sharing and interoperability between each other to ensure transparency of opioid use across state lines.

18





Argoff

Those of you with patients on Medicaid are aware of its lock-in program, which provides some ideas on how to limit abuse as well.

Federal law allows Medicaid to restrict patients who overutilize Medicaid services to designated providers. It does so by requiring a patient to be seen by one HCP and obtain their prescriptions from a single pharmacy.

The purpose of this is to empower a single provider to coordinate care, to reduce doctor and pharmacy shopping, to limit drug diversion, and to reduce healthcare utilization and


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		<p>pharmacy cost. Now this might be adopted by other governmental payers beyond Medicaid and even by private insurers as well to accomplish the same purposes.</p>
19		<p>Argoff</p> <p>As we alluded to earlier, opioid scheduling can also help address prescription opioid abuse. As you know, the lower the number, the higher the potential for abuse and dependence.</p> <p>Hydrocodone products were rescheduled from Schedule 3 to Schedule 2 in late 2014, which makes the process of obtaining a prescription and refills somewhat more difficult.</p>
20		<p>Argoff</p> <p>The US Food and Drug Administration has also established a series of steps designed to help reduce opioid-related risks, and these are known collectively as opioid risk evaluation and mitigation strategies, or REMS.</p> <p>They include the establishment of a medication guide or patient package inserts, a communication plan, one or more elements to assure safe use, an implementation system and a timetable for reporting the REMS assessments to see if these strategies have been effective or not.</p>

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21	<p>REMS Programs Differ by Opioid Class</p> <p>IR Opioids¹</p> <ul style="list-style-type: none"> No REMS Required <p>ER/LA Opioids²</p> <ul style="list-style-type: none"> Practitioner participation not mandatory Access not restricted <p>TIRFs³</p> <ul style="list-style-type: none"> Practitioner and manufacturer participation mandatory Restricted access <p><small>REMS: risk evaluation and mitigation strategy. 1. IR: immediate-release (IR) opioids. 2. ER/LA: extended-release (ER/LA) opioids. 3. TIRF: transdermal immediate-release fentanyl (TIRF). 4. L.A. Pain and Drug Administration: https://www.lapainanddrugadministration.com/news/for-practitioners/understanding-the-rems-program-for-extended-release-opioids/2017/04/04/ Accessed July 16, 2019. 5. L.A. Pain and Drug Administration: https://www.lapainanddrugadministration.com/news/for-practitioners/understanding-the-rems-program-for-transdermal-immediate-release-fentanyl/2017/04/04/ Accessed July 16, 2019. 6. L.A. Pain and Drug Administration: https://www.lapainanddrugadministration.com/news/for-practitioners/understanding-the-rems-program-for-transdermal-immediate-release-fentanyl/2017/04/04/ Accessed July 16, 2019.</small></p>	<p>Argoff</p> <p>REMS programs differ by opioid class. For example, immediate-release opioids do not require a risk evaluation and mitigation strategy program per FDA guidelines. The transdermal immediate-release fentanyl products or TIRF do involve a REMS program and practitioner and manufacturer participation is mandatory, with access restricted to prescribers who have completed certain educational activities and have scored successfully on an examination.</p> <p>In other words, not everyone with a DEA number can prescribe this medication. There has to be an additional set of educational activity before that can happen.</p> <p>With extended-release and long-acting opioid therapy, participation in the REMS program is not mandatory for the practitioner and access is not restricted to prescribers who have fulfilled certain criteria.</p>
22	<p>Recent FDA Labeling Changes for ER/LA Opioids</p> <p>INDICATION CHANGE #1</p> <p>ER/LA opioids are indicated for management of pain severe enough to require daily, around the clock, long-term opioid treatment and for which alternative treatments are inadequate</p> <p>INDICATION CHANGE #2</p> <p>Should be reserved for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain</p> <p>POST-MARKETING STUDIES</p> <p>FDA requires new studies to further assess the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death</p> <p>NEW BOXED WARNING</p> <p>Chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS)</p> <p><small>4. L.A. Pain and Drug Administration: https://www.lapainanddrugadministration.com/news/for-practitioners/understanding-the-rems-program-for-extended-release-opioids/2017/04/04/ Accessed July 16, 2019.</small></p>	<p>Argoff</p> <p>The federal government, through the FDA, can also change what's in the package insert of a product. Here, you see some recent changes in the package inserts of extended-release opioids.</p> <p>As you can see, the indication itself for extended-release and long-acting opioids has changed in two ways.</p> <p>The first change specifies that extended release or long-acting</p>

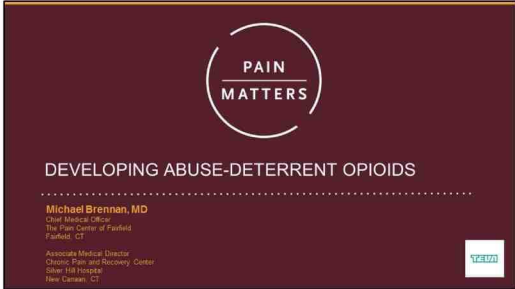

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		<p>opioids are indicated for management of pain severe enough to require daily around the clock, long-term opioid treatment and for which alternative treatments are inadequate.</p> <p>The second change states that these agents should be reserved for use in patients for whom alternative treatment options (for example, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated or are otherwise inadequate to provide sufficient management of pain.</p> <p>There are also post-marketing studies the FDA now requires. The FDA specifically is requiring new studies to further assess the known serious risks of misuse, abuse, and increased sensitivity to pain (sometimes known as hyperalgesia), addiction, overdose, and death.</p> <p>Finally, there is also a new boxed warning that states “chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome or NOWS.”</p>
23		<p>Argoff</p> <p>To summarize, we need to really consider a multifaceted approach to addressing opioid abuse. The key stakeholders in this multifaceted approach include healthcare providers, patients, and government. As we discussed, healthcare provider strategies for mitigating opioid abuse include universal precautions, screening for drug abuse and abuse risk, urine testing, and adherence</p>

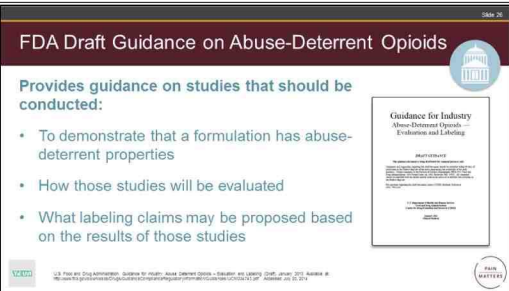
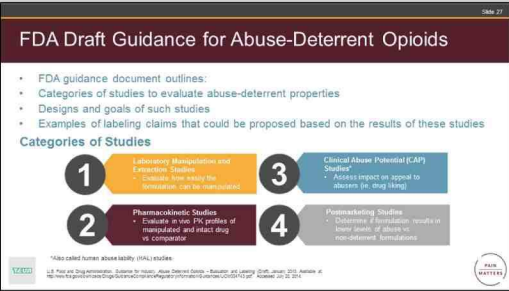
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	<p>monitoring.</p> <p>Patients should also be educated, specifically on the methods and importance of safe use, safe storage, and safe disposal of opioids.</p> <p>The Federal and State government have developed and continue to develop programs aimed at making opioid diversion and abuse more difficult and less likely including the use of prescription drug monitoring programs, the risk evaluation and mitigation strategy programs or REMS, and labeling changes.</p> <p>I hope you enjoyed this chapter of the program and better understand the role that HCPs, patients, and the government play in a multifaceted abuse mitigation strategy.</p> <p>I also want to suggest that industry may play a role in helping mitigate opioid abuse. To tell you a little more about this and the potential role of abuse deterrent opioids, please watch the final chapter in this series presented by Dr. Michael Brennan.</p>
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Part 4 – Developing Abuse-Deterrent Opioids	
24	<div>  </div> <div> <p>Brennan</p> <p>I'm Michael Brennan and I'm the medical director and chief medical officer of the Pain Center of Fairfield in Fairfield, Connecticut.</p> <p>I'm also associate medical director for the Chronic Pain and Recovery Center at the Silver Hill Hospital in New Canaan, Connecticut.</p> <p>Over the previous chapters in this program, you heard about some of the issues associated with opioid use and how HCPs, patients, and the government can help reduce risks associated with opioid therapy.</p> <p>Now, I'm going to tell you about the potential role that the pharmaceutical industry might play in mitigating opioid abuse, specifically through the development of abuse-deterrent opioids.</p> </div>
25	<div>  </div> <div> <p>Brennan</p> <p>You'll see that there are 5 general approaches that have been recognized by the FDA as categories of abuse deterrent opioids. These include physical/chemical barriers, antagonist combinations, aversion substances added to the analgesic, delivery system characteristics, and finally, pro-drugs.</p> <p>Each one of these will be discussed in detail a little further on with how the FDA will be testing the abuse deterrent qualities, but keep in mind that all of these products, no matter how they're made, have to have a key</p> </div>


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		<p>component, which is: when the drug is not altered or when the delivery system is not altered, the medicine works as well for pain with comparable side effects to a drug that does not have abuse deterrent characteristics.</p> <p>So that's the technical issue, right? Creating a drug that will work for pain, but at the same time making it difficult for somebody to want to abuse that drug or make abusing the drug less beneficial.</p>
26		<p>Brennan</p> <p>So where does the industry get their ideas on how to do this? There was a guiding principle document known as the Draft Guidance on Abuse Deterrent Opioids that was published by the FDA in 2013.</p> <p>Anyone who is interested in getting the background on abuse deterrents should review this so they could see the hard work that's gone into it both from the pharmaceutical industry, as well as government oversight agencies.</p>
27		<p>Brennan</p> <p>There are several study types that companies will need to subject their products to in order to enable the company to make claims in the package insert. And for those of us who see pharmaceutical reps or go to programs, we know how important this will be for getting the message across to clinicians about abuse deterrents.</p> <p>So there are four general types of studies that need to be done to get the ultimate label of a true abuse</p>

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	<p>deterrent opioid. Now, typically we think that in a sequential series, one, two, three and four, things would follow each other, but it's very important to notice as we look through these studies that they don't necessarily build upon each other.</p> <p>And as we go into the types of abuse deterrent technologies, it'll become clear that certain technologies may meet one type of study and prove beneficial, but not necessarily a different type.</p> <p>The first kind of studies are the laboratory manipulation and extraction studies. These determine if tampering with the drug can override the formulation and provide access to the unadulterated opioid.</p> <p>The next are the pharmacokinetic studies. These look at how the normal drug works when it's been taken by the individual, whether the capsule or the aversion or the antagonist that's been added has any direct effect on the intended pharmacokinetic effect of the drug, and after the drug has been manipulated in the lab, if there is any alteration in the pharmacokinetics.</p> <p>For example, if there is an increased availability of the drug or if there is a shortening to peak plasma concentration.</p> <p>These studies are key because for many of us, pharmacokinetics are linked with the pharmacodynamic effect of the drug.</p>
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		<p>The third type of test is the clinical abuse potential study. These are studies that look to see how the drug in its unaltered and altered state is viewed by recreational drug users.</p> <p>Finally, and perhaps the greatest hurdle, will be the post-marketing studies. Has there been a demonstrable reduction in abuse based upon the availability of a certain drug in the market? As you can imagine, it's going to take several years to determine if there's been a positive effect.</p>
28		<p>Brennan</p> <p>Now, there are four tiers of label claims that can be achieved and put into the package insert.</p> <p>The first is that the medication has been formulated with a physiochemical barrier to abuse.</p> <p>Another claim is that the drug is expected to reduce or block the effect of the opioid when the product is manipulated.</p> <p>The third is that the medication is expected to result in a meaningful reduction in abuse and finally, the fourth tier that everyone will be trying to achieve, is that the formulation has been shown to reduce abuse of the opioid molecule in the community.</p>

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Brennan

Let's look carefully at the manipulation studies that have been put forth by the FDA. The goal of this type of study is to see, through physical or chemical manipulation, if a drug can be easily extracted from the formulation.

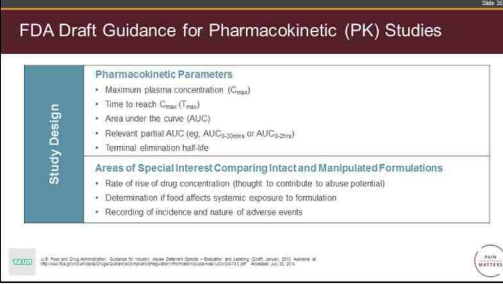
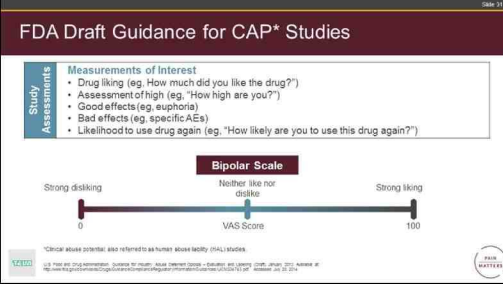
So the goal is to look at particle size and determine if a small enough particle of active drug can be extracted through various methods (including crushing, grinding, hammering, chemical reactions, and changing temperature). In other words, think of whatever a closet chemist might try to do to get that active drug out of the delivery system.

Let me emphasize this again. Remember, the molecules we're using are the same 13 or so molecules that are available in the United States that are deemed opioid analgesics. So it's not the molecule really. What we're looking at are the formulations carrying those molecules. Can those formulations protect and make it so the drug is less likely to be used in ways other than intended?

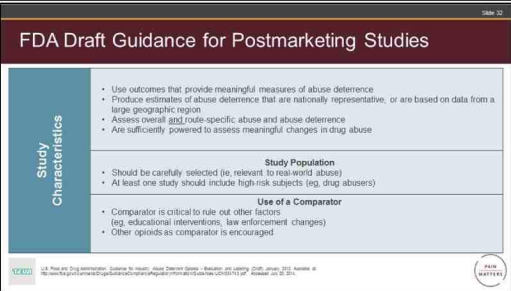
And the studies also include, as I mentioned, solubility studies and we're trying to target three specific means of abuse: snorting, smoking, and injecting. Why are these three the types mentioned by the FDA? Because these are the approaches that more often linked to substance abuse and addiction.

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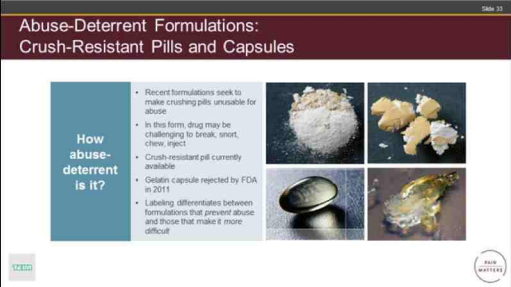
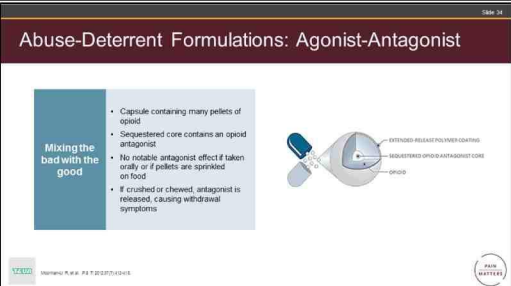
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30	 <p>FDA Draft Guidance for Pharmacokinetic (PK) Studies</p> <p>Study Design</p> <p>Pharmacokinetic Parameters</p> <ul style="list-style-type: none"> Maximum plasma concentration (C_{max}) Time to reach C_{max} (T_{max}) Area under the curve (AUC) Relevant partial AUC (eg. $AUC_{0-20hrs}$ or $AUC_{0-24hrs}$) Terminal elimination half-life <p>Areas of Special Interest Comparing Intact and Manipulated Formulations</p> <ul style="list-style-type: none"> Rate of rise of drug concentration (thought to contribute to abuse potential) Determination if food affects systemic exposure to formulation Recording of incidence and nature of adverse events 	<p>Brennan</p> <p>The second types of studies that I mentioned earlier are the PK studies. So for those of you who can remember back to medical school, pharmacokinetics look at how a drug acts in the system by looking at plasma concentration.</p> <p>So we're interested at looking at maximum plasma concentration, the time to reach this maximum, the total area under the curve, a relevant partial area under the curve, which we think is very important in substance abuse that is, how quickly does the drug get absorbed and how much is absorbed in 30 minutes and up to 2 hours, and then what's the terminal elimination half-life?</p> <p>What's very important in these trials is to try and understand if manipulation of the drug has an effect on the rate of rise of drug concentration. We want to determine if other substances, benign substances (food, alcohol, water, other common solutions, such as soda) might affect the way the drug is ultimately absorbed and what effect they might have, and also record the incidence of adverse events.</p>
31	 <p>FDA Draft Guidance for CAP* Studies</p> <p>Study Assessments</p> <p>Measurements of Interest</p> <ul style="list-style-type: none"> Drug liking (eg. "How much did you like the drug?") Assessment of high (eg. "How high are you?") Good effects (eg. euphoria) Bad effects (eg. specific AEs) Likelihood to use drug again (eg. "How likely are you to use this drug again?") <p>Bipolar Scale</p> <p>Strong disliking — Neither like nor dislike — Strong liking</p> <p>0 — VAS Score — 100</p>	<p>Brennan</p> <p>Let's take a look at what are known in the draft guidance as CAP, or Clinical Abuse Potential, studies. These are what we used to refer to as the Human Abuse Liability potential of a drug, measured in a way that many clinicians find interesting.</p> <p>It's basically exposing recreational non-dependent individuals to the</p>

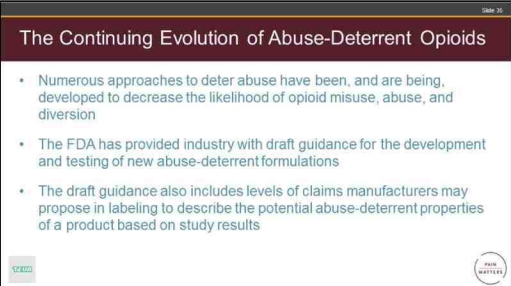
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		<p>opioid formulation. So people who aren't physically dependent on an opioid, but will use them recreationally and have enough experience to understand what the normal high of an opioid would feel like.</p> <p>And what the subjects are asked to do is tell us how much they like the drug. So they're given a visual analog scale, sometimes it's a 0 to a 100 or it's a strong dislike to a strong liking similar to this bipolar scale on the slide where the individual is asked after being exposed to the drug how much they like it or dislike it.</p> <p>And they're asked questions, questions that you and I won't ask in our clinics, like how high are you, what's the euphoria like? I mean, we may ask our patients about adverse events, but here we're trying to tease out different information from these recreational drug abusers and then the all-important question, how likely are you to abuse this drug if you can get it?</p>
32	 <p>Study Characteristics</p> <ul style="list-style-type: none"> Use outcomes that provide meaningful measures of abuse deterrence Produce estimates of abuse deterrence that are rationally representative, or are based on data from a large geographic region Assess overall and route-specific abuse and abuse deterrence Are sufficiently powered to assess meaningful changes in drug abuse <p>Study Population</p> <ul style="list-style-type: none"> Should be carefully selected (ie, relevant to real-world abuse) At least one study should include high-risk subjects (eg, drug abusers) <p>Use of a Comparator</p> <ul style="list-style-type: none"> Comparator is critical to rule out other factors (eg, educational interventions, law enforcement changes) Other opioids as comparator is encouraged 	<p>Brennan</p> <p>The FDA also notes that pharmaceutical manufacturers can conduct post-marketing studies in order to examine if a formulation is likely to decrease abuse in the community.</p> <p>The goals are to try and provide estimates of how the drug is being abused, whether it's being snorted or injected, and has this formulation demonstrated a reduction in abuse.</p> <p>These studies require sufficient</p>

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		<p>numbers to determine whether or not there is a real or an artificial effect, and as such, study populations are going to have to be carefully selected to target real-world abusers.</p> <p>Comparators will also be looked at to see if changes are due to the formulation or other factors, like public service announcements and education of consumers and clinicians. There will also likely be other opioid comparators as part of these studies.</p>
33		<p>Brennan</p> <p>Now that we've reviewed the studies that may be conducted to test an abuse-deterrent opioid formulation, let's switch gears and look at some of the different approaches.</p> <p>Perhaps the most common form of abuse deterrent is the crush-resistant pills and capsules. All of these have in common a process that makes it either very difficult to crush the pill, or as we see in the bottom right picture on this slide, a pill that if crushed becomes a viscous or gelatinous substance that's very difficult, if not impossible, to draw up in a syringe or to snort.</p>
34		<p>Brennan</p> <p>Here we see a different approach, which is the use of agonist/antagonist combinations.</p> <p>For example, in a medication with a sequestered opioid antagonist core, the antagonist will only be released if the formulation is manipulated. If the product is tampered with, however, the sequestered antagonist is released, countering the effects of</p>

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		<p>the opioid.</p> <p>Regardless, we still have to ask, are either of these approaches going to prevent abuse entirely? Only time will tell following the widespread use of abuse-deterrent medications.</p>
39		<p>Brennan</p> <p>In summary, different approaches to opioid deterrence continue to evolve. As I mentioned earlier, there are aversive technologies, there are pro-drugs that may become available. This is a very exciting science and a very exciting time to offer our patients drugs that may make the abuse of their drugs more difficult, and may help potentially reduce some of the stigma of taking pain medicines.</p> <p>It will take time to work through the testing, especially the epidemiological testing, but as these studies are completed and reviewed by the FDA, abuse-deterrent opioids will be able to include language in their package inserts to let clinicians know what effect the formulation is likely to have on abuse and abuse potential, which will ultimately help us make better informed decisions for our patients.</p> <p>Thank you for watching this chapter on the development of abuse-deterrent opioids. If you haven't already, please be sure to return to the main menu to watch the other chapters, including Jeff Gudín talking about the complexities we face in pain management, and Charles Argoff discussing a Multi-Faceted Approach to Address Prescription Opioid Abuse.</p>

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		On behalf of all 3 faculty and Teva Pharmaceuticals, we hope you enjoyed the program and thank you for your time.
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